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FACTORS IN REACTIVATION OF DRUG-TREATED INACTIVE PULMONARY TUBERCULOSIS

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FACTORS IN REACTIVATION OF DRUG-TREATED INACTIVE PULMONARY TUBERCULOSIS

by

Robert A. Gunn

A Thesis Submitted to the
Faculty of the
Yale University School of Medicine
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Degree of Doctor of Medicine

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INTRODUCTION

The purpose of this study is to evaluate determinants which may be important in reactivation of previously drug-treated, inactive cases of pulmonary tuberculosis. Since the advent of chemotherapy in the treatment of tuberculosis, reactivation rates of treated cases have declined from approximately 25% in the 1940's to just under 5% at present. Prior to the advent of chemotherapy, there were numerous factors which predisposed to reactivation among which the most important were 1) extent of disease, (Appendix I), 2) duration of hospitalization, and 3) patient cooperation. However, since the widespread use of anti-tuberculosis drugs in the treatment of tuberculosis during the past 15 years, little attention has been directed to the factor or factors currently leading to reactivation of disease.

REVIEW OF THE LITERATURE

Before the use of chemotherapeutic drugs in the treatment of tuberculosis, it was estimated that 15-25% of cases of pulmonary tuberculosis became reactivated. In many reports, however, these data pertained more to relapse than to reactivation since these studies included many patients who left the hospital and later re-entered before they had become inactive according to the present acceptable standards of the National Tuberculosis Association. Relapse is, therefore, unfortunately a nebulous term that often includes true reactivation but also is used for exacerbation of pulmonary disease that only seemed stabilized. Reactivation for the purposes of this study is defined on page 9.

In 1954, Lincoln, et. al.[1], reported the results of the study of

of patients in the Herman Biggs Hospital in New York State during the period of 1937-47. These investigators found that relapse rates correlated well with the original extent of pulmonary disease. It was determined that during the first 3 years following discharge the relapse rate was 2.9% for 448 patients with minimal disease; 5.8% for 224 patients with moderately advanced disease; and 10% for 269 patients with far-advanced disease. These patients were not treated with chemotherapy. After 3 years, the rate of relapse was 5.3% for patients with all three categories of disease, i.e., minimal (P1), moderately advanced (P2), and far-advanced (P3). These data correlate well with other studies which also showed that the greater the extent of the original pulmonary disease, the higher the percentage of relapse.

Boyum[2] in Norway in 1958, in a comprehensive review of the world literature on relapse, reported some important facts. Boyum reported that in the United States a review of 1213 patients by M. G. Stephens[2] during the 1914-44 period reported the following relapse rates: in patients with minimal lesions, 28% of males and 15% of females relapsed; in those with moderate lesions, 37% males and 23% females relapsed; far-advanced lesions, 41% males and 19% females relapsed. These data not only demonstrated that relapse is more common in the far-advanced group, but also that there was a predominance in males in this category. Stephens' data also showed that relapse was not influenced by age. Other reports (Oyama, 1955[2]; Mitchell, 1955[2]) have shown that relapse was twice as common in patients with bilateral disease as compared to those with unilateral disease. However, size of cavitation seemed to have no bearing on relapse. It was also shown by many authors (Griep, 1940[2]; Stephens, 1954[2]; Paine, 1951[2]) that the longer patients remained in the sanatorium and the longer their x-rays were stable in the

sanatorium, the less likely they were to relapse.

Boyum[2] studied 439 cases of relapsed diseases who were admitted to one sanatorium in Norway between 1946 and 1956. All of these patients were symptom free from their original disease at the time of their first discharge from hospital. He also found relapse more common in patients with advanced disease. In patients with bilateral disease, relapse was twice as common as those with unilateral disease. Boyum also noted that in the upper socio-economic class, the relapse rate was only 2.3% which he attributed to better living conditions and freedom from manual labor in the upper socio-economic group. He also found that men had a slightly greater tendency to relapse than women; and that 75% of relapses in both sexes occurred during the first 5-year period after hospitalization.

In a current textbook by Walter Pagel, Pulmonary Tuberculosis[3], various factors were mentioned which predispose to activation of a primary focus or a secondary clinically inapparent inactive focus, both of which were not previously treated. These patients are those who are tuberculin positive, but who never had clinically apparent pulmonary tuberculosis. Activation of disease in these groups is more common in older age groups, and it is suggested that such factors as tissue aging, endocrine factors, inadequate diet, etc., may be of importance in age distribution. The importance of nutrition is emphasized by findings that the rate of tuberculosis in people whose weight is only 85% of normal is 14 times greater than those who are normal in weight. Endocrine factors also seem to play a role in activation of tuberculosis, and it has been recognized that use of steroids increase such activation and that the control of tuberculosis infections is more difficult in patients having diabetes mellitus.

The advent of chemotherapy of tuberculosis began in 1947 with the widespread use of streptomycin. This antibiotic was discovered by Schatz,

Waksman, and Brigie[4] in 1944 after extensive experimentation with products of soil actinomycetes. Streptomyces griseus produced this product, streptomycin, which was found to be a potent, relatively non-toxic antibiotic. The exact mode of action of streptomycin is not known, and at present the most generally accepted theory is that it interferes with protein synthesis (Davies, et. al., 1964[4]). The activity of streptomycin is both bacteriostatic and bacteriocidal for the tubercule bacillus in-vitro, but in-vivo it is mainly suppressive. However, it has been found that when the drug is used alone , resistant strains of bacilli develop rapidly. In addition, the drug has the disadvantage of being frequently allergenic; the most common manifestations being fever, skin rash, and eosinophilia.

Also in 1947, para-aminosalicylic acid (PAS) was introduced in the treatment of tuberculosis infection. The mode of action of PAS seems to be one of competition with para-aminobenzoic acid (PABA), an essential requirement for growth of bacteria. This drug is used in combination with other tuberculostatic drugs mainly streptomycin and isoniazid, since it is very ineffective when used alone. Although para-aminosalicylic acid is also allergenic, it is less so than streptomycin, and the most important untoward reactions with PAS are gastrointestinal symptoms including nausea, vomiting, epigastric distress, and diarrhea. Although PAS is closely related chemically to the salicylates, it possesses none of the pharmacologic effects of salicylates.

At the present time, the most effective anti-tuberculous drug is isoniazid which was first used in 1952. The action of isoniazid has been found to be both bacteriostatic and bacteriocidal in in-vitro testing. When used alone, resistant strains of bacilli to isoniazid may emerge within a few weeks, but this time may vary.[4]. Also in many cases, even though the bacilli are shown to be resisant by in-vitro testing, the efficacy of

therapy is not reduced.[5,6] Isoniazid is well tolerated without noticeable side effects unless the drug is administered in large doses. The most frequent toxic manifestation is that of a peripheral neuropathy which is reversed by the administration of Pyridoxine. When isoniazid is used in combination with PAS and/or streptomycin, it is a highly effective chemotherapeutic agent, and the development of bacterial resistance is delayed considerably.

These three drugs then, isoniazid, PAS, and streptomycin, are the major chemotherapeutic agents used in the current treatment of tuberculosis. Treatment for pulmonary tuberculosis varies from 1 - 3 years, the average being 2 years. Often after the disease process has been stabilized, PAS and streptomycin are discontinued, and chemotherapy with isoniazid alone is continued. Clinically, studies have repeatedly shown that when these drugs are used properly, treatment failures develop in less than 5% of cases.[7]

Since the advent of chemotherapy in the treatment of pulmonary tuberculosis, relapse rates have declined sharply. At the West Haven Veterans Hospital, West Haven, Connecticut, D'Esopo, et. al.,[5] found the observed relapse rate over the last ten years to be less than 4%. In a study by Phillips[8] at the Kennedy Veterans Hospital, Memphis, Tennessee, in 1961, a six-year follow-up of 109 patients showed a relapse rate of 8.5%. In the Madras study in Madras, India, the relapse rate of 107 patients who received only one year of chemotherapy was only 9%.[9] It is now generally accepted that approximately 5 per cent of treated cases of pulmonary tuberculosis reactivate.

Many aspects of the treatment of tuberculosis have recently been investigated at the Tuberculosis Center in Madras, India.[9,10,11,12,13] In a recent study at this institution, therapeutic results were compared in

regard to home versus sanatorium treatment. Eighty-two (82) patients, 49 males and 33 females, were treated at home and were compared to eighty-one (81) patients, 50 males and 31 females, who were treated in the sanatorium. Chemotherapy was the same in each group of patients who received a mean daily dosage of 4.6 mgms/kg of body weight of isoniazid and .23 gms.kg of body weight of PAS. It was observed that patients who were treated at home received substantially inferior diets compared to those in sanatoria. For example, forty-nine per cent of 79 home patients who were assessed had a daily calorie intake of less than 2,000 calories compared with four per cent of 78 sanatorium patients ($P < 0.001$). At the end of one year of treatment, 92% of the sanatorium patients and 86% of the home patients had quiescent disease, which was defined in this study as negative sputum examinations for the last 3 months of treatment. This small difference is not statistically significant. After one year of treatment at home and in the sanatorium in Madras, 126 patients who had quiescent disease were randomly allocated into two groups to be treated at home for one year: one group of 65 patients received isoniazid; the other group of 61 patients received calcium gluconate placebo medication. Results of this study showed that isoniazid seemed to have no effect upon relapse of those cases where there was persistent cavitation (open negative case), but it was effective in preventing relapse in those quiescent cases where there was no residual cavitation. In 42 patients with non-cavitary quiescent disease, who were treated for an additional one year with isoniazid alone, there were no bacteriological relapses. In a similar group of 42 patients treated with placebo, there were 5 relapses. This difference is statistically significant ($P < .05$). These results are supported by the results of a combined study of the above 42 patients and a similar group of 61 patients. In these

combined 103 patients with non-cavitary quiescent disease, the relapse rate was 0% among those receiving isoniazid and increased to 9% in the placebo-treated group. This is a highly significant difference, ($P < 0.005$). Another group, 60 patients, who had quiescent disease at the end of two years and had been treated for two years, were continued on therapy to determine the efficacy of 3 years of treatment as compared to 2 years. These 60 patients were randomly allocated into two groups of 30 patients. At the end of the year, no relapses had occurred in either group. It was concluded from these studies that when patients develop quiescent disease at the end of one year of treatment with isoniazid and PAS, further isoniazid therapy for an additional two years helped to prevent relapses only in those patients who did not have residual cavitary disease. The results of the five-year follow-up of those patients should provide valuable information.

Recently, in the United States, Katz, et. al.,[14] studied the effect of an additional 2 years of isoniazid therapy on inactive previously drug-treated cases of pulmonary tuberculosis. These investigators found that in 129 previously drug-treated inactive cases, the reactivation rate was 2.5% as compared to 5.4% in the control group who received a placebo medication.

At the present time, no large scale studies concerning factors which may play a role in reactivation of pulmonary tuberculosis, treated by currently accepted measures, have been conducted. The consensus of opinion of many physicians who are working in this field and in particular those involved in the Madras study[15], is that cure and prevention of reactivation is dependent on four factors: 1) adequate chemotherapy, 2) duration of chemotherapy, 3) patient cooperation, and 4) initial drug sensitivity; and conversely, reactivation seems to be independent of age, sex, and extent of disease.

MATERIALS AND METHODS

This project consists of a follow-up study of 40 reactivated cases of pulmonary tuberculosis and 40-non-reactivated control cases who were selected from the records of the Mt. Morris Tuberculosis Hospital in Mt. Morris, New York. Mt. Morris Hospital is located in western New York state and presently serves the entire western part of the state, encompassing 15 counties. This hospital has a capacity of 350 beds and presently the average census is approximately 250 patients. The hospital is staffed by ten physicians, two surgeons, a part-time pathologist, a full-time radiologist, and a fully equipped laboratory. The out-patient department primarily serves Livingston County through the hospital and in addition the staff visits a major city in the ten outlying counties on a monthly basis.

All new cases admitted to the hospital are presented to the director and the medical staff of the hospital. X-rays are reviewed by the hospital radiologist and are again considered when the case is presented to the medical staff. Decisions regarding chemotherapy, activity of disease, and hospital discharge of patients are made at weekly staff conferences, where x-rays are again reviewed.

In this study, all diagnoses dependent upon radiologic interpretation, i.e. , emphysema, silicosis, and cavitary lung lesions were reviewed at my request with a member of the house staff or the director. This procedure was followed in all cases of emphysema, silicosis, and in those cases reported as questionable cavitary lesions. In most cases, diagnosis of emphysema was a combination of clinical and radiologic interpretation, for there were no pulmonary function tests performed in mose cases.

CRITERIA FOR SELECTION OF STUDY GROUP AND CONTROLS

To be included in this study, the reactivated patients must have been

hospitalized and treated with chemotherapy for control of their pulmonary tuberculosis. They then must have reached an inactive status defined by the National Tuberculosis Association which specifies: 1) a negative sputum examination for a minimum period of 6 months, 2) a stable chest x-ray for a minimum period of 6 months, and 3) no evidence of pulmonary cavitation or bronchopleural fistulae (see Appendix II). The diagnosis of pulmonary tuberculosis was made on the basis of 1) a positive sputum culture (human M. Tuberculosis var hominis), 2) radiologic evidence of pulmonary tuberculosis, and/or 3) a compatible clinical picture. All patients were treated with chemotherapy, either with a program consisting of isoniazid and adjuvant drugs, or with a program without isoniazid, which included mainly PAS and streptomycin. The majority of these patients were initially treated at Mt. Morris, although a few were treated at other regional hospitals. All patients were followed in the Mt. Morris out-patient department. Because of the difficulty in selecting cases considered to be true reactivations of pulmonary tuberculosis, the 40 patients in this test group are the only true reactivated cases which could be uncovered in a review of records of the past 15 years at Mt. Morris Hospital.

The most important criterion of reactivation of pulmonary tuberculosis is the development of a positive sputum examination after previously demonstrated inactivity of the tuberculous infection. In most cases in this study, patients developed two or more positive sputum examinations and demonstrated recent x-ray changes and/or associated clinical symptoms. In these few cases where there was only one positive sputum examination, it was necessary that radiologic changes and/or clinical symptoms be demonstrated in order to consider the patient as having reactivated disease. Therefore, a patient having only a single positive sputum examination without additional evidence

of disease was not considered to be a reactivated case because this situation could represent a laboratory error or a chance finding, and it is probably neither clinically nor epidemiologically important. All study patients reactivated within five years after reaching the inactive status.

The matched control group is composed of persons, who like the study group, had developed pulmonary tuberculosis diagnosed on the basis of the following criteria: 1) a positive sputum examination, 2) radiologic evidence and/or 3) associated clinical picture. These patients had also been treated with hospitalization, chemotherapy and in some cases resectional surgery. The control patients had reached an inactive status and had remained so for at least five years. They were also followed regularly in the outpatient department of Mt. Morris Hospital and had received at least yearly chest x-rays and sputum examinations. In all control cases, sputum examinations remained negative and the x-ray findings revealed no essential changes. If, as was the case in a few individuals, radiologic change was demonstrated, but this was not associated with the demonstration of a positive sputum examination, the patient was still considered to have inactive disease.

SELECTION OF PATIENTS AND CONTROLS FOR STUDY AND COLLECTION OF INFORMATION

Patients with reactivated pulmonary tuberculosis were selected for this study by a review of all hospital records of the Mt. Morris Tuberculosis Hospital during the past 15 years. Cases were reviewed by first examining the discharge index card on each patient and then reviewing the corresponding chart. Controls were selected by also reviewing the discharge index cards. The control patients were included in the study by matching with the study group patients in five categories: 1) age, 2) sex, 3) race, 4) use of resectional surgery, and 5) presence or absence of isoniazid in

the chemotherapy regimen, and if they had a five-year follow-up study confirmed by continuing inactivity. No other factors were considered in selecting the control patients. The records of each patient were reviewed through the use of a 12-page information sheet as a basic outline for obtaining information. The areas that were investigated can be divided into three main areas: 1) the general characteristics, history, and admission data, 2) observation in the hospital, and 3) observation after discharge from the hospital. The areas that were emphasized in this study pertained to length of hospitalization, length of active disease, sputum culture patterns, conversion time under chemotherapy, the amount and length of drug therapy, and the post discharge conditions. The results obtained in these areas of study and others are reported and discussed in this paper.

In this study, there were no patient interviews, and all information was gathered from the written record. The hospital course of the patient was only discussed with the physician in charge when the written record was unclear. This procedure, however, was not often necessary because the records at Mt. Morris Hospital are typewritten and follow a standard format.

RESULTS

GENERAL CHARACTERISTICS, HISTORY, AND ADMISSION DATA OF STUDY AND CONTROL GROUPS:

The reactivated and control groups are composed of 40 patients each. The characteristics of these cases by age are recorded in Tables 1 and 2. The study group of reactivated cases and control group were matched in five categories: 1) age, 2) sex, 3) race, 4) use of resectional surgery, and 5) presence or absence of isoniazid in the chemotherapy regimen.

The age in years designated for each patient is the age at which inactivity of disease was attained. The mean age of the study group is

57.07 years with a range of 20 to 88 years while the control group had a mean of 55.62 years with a range of 16 to 75 years.

In regard to marital status, as depicted in Table 3, 10 patients (25%) in the study group were either divorced or separated. In the control group, 5 patients (12.5%) had been either divorced or separated. However, this finding was not statistically significant (P=.14).

Patients in both groups were evaluated for concomitant disease which was present prior to the time they developed tuberculosis and persisted during the treatment of their pulmonary tuberculosis. Many of these disorders are chronic diseases, and there was no reliable way to determine their severity in an objective fashion. The diagnosis of concomitant disease was made by the examining physician at the time of admission or by appropriate tests performed during the hospital course. Those patients with emphysema and silicosis were reviewed radiologically for evidence of disease. Unfortunately, no pulmonary function tests were available for most of these patients. As shown in Tables 4 and 5, 13 patients (32.5%) in the study group had pulmonary emphysema whereas, 10 patients (25.0%) in the control group had pulmonary emphysema. The prevalence of diabetes mellitus, silicosis, or extra-pulmonary tuberculosis was the same in both the study and control groups.

All patients were evaluated for the presence or absence of respiratory symptoms of tuberculosis at the time of admission to the hospital. These symptoms included cough, shortness of breath, chest pain, hemoptysis, etc. In the study group, 35 patients (90%) had respiratory symptoms whereas, 32 patients (80%) in the control group had such symptoms.

A past history of tuberculosis documented by positive sputum, clinical symptoms, and hospitalization were compared in patients in both groups.

In none of the patients had anti-tuberculous chemotherapy been used. Ten patients (25%) in the study group had a past history of tuberculosis whereas, in the control group 7 patients (17½%) had a positive history. This information regarding previous tuberculosis infection was obtained by the admitting physician and in some cases by clinical reports from other hospitals which were forwarded to Mt. Morris Hospital. In general, however, the information lacked specificity and no meaningful comparisons could be made between patients in both groups in regard to duration of past episodes, time between last clinically evident tuberculosis and present tuberculosis, etc.

When patients are admitted to the hospital, the extent of their pulmonary disease is determined by radiologic examination. The extent of disease is determined in accordance with NTA definition (see Appendix I), and is classified as minimal (P1), moderately advanced (P2), or far-advanced (P3). Radiologic examinations also determine the presence or absence of cavitation. If cavitation is present, the extent of disease is considered to be at least moderately advanced (P2). Patients in both groups were classified in this study in relation to the extent of their disease according to the most advanced extent attained and were compared. As depicted in Table 6, both study and control groups had a similar number of cases having minimal, moderately advanced, and far-advanced disease.

The presence of bilateral and unilateral pulmonary disease was also compared in both groups. It was noted that bilateral disease was present in 25 patients (62.5%) in the study group and in 27 patients (67.5%) in the control group. These results are shown in Table 7. Cavitary disease was present in 20 patients (50%) in the study group and in 19 patients (47.5%) in the control group as shown in Table 8.

Due to the lack of specific information, patients were not compared in regards to occupation, smoking habits, drinking habits or educational background.

OBSERVATIONSOF HOSPITALIZED PATIENTS AND CONTROLS

A. DAYS OF HOSPITALIZATION

In regard to the number of days of hospitalization, it was found that the 40 study cases were hospitalized for periods ranging from 65 to 3240 days with a mean of 479 days. Similarly, the control group was hospitalized for intervals of 35 to 2070 days with a mean of 477 days. There is no significant difference between the two groups.

It is recognized, however, that for a variety of reasons in-patients hospitalization treatment of cases of pulmonary tuberculosis is not always continuous and patients may leave the hospital temporarily for a variety of reasons. For the purpose of these analyses, a break in continuity of hospitalization is defined as a period of time of greater than 10 days away from the hospital. In the study group, 6 patients (1 woman and 5 men) or 15% were absent from the hospital while their disease was active. These absences ranged from 30 to 510 days with a mean of 184 days. During this time, however, only one patient (a 66-year old man) discontinued chemotherapy; and this was for a period of 240 days. Among the 40 control patients, 5 men (12.5%) were absent from the hospital for intervals ranging from 21 to 60 days with a mean of 37 days. During these absences, all 5 patients discontinued chemotherapy.

B. ACTIVITY OF DISEASE

The length of time that the disease remained active was evaluated in each group. Active disease is defined as the length of time between the first positive sputum or the onset of symptoms which later were proved to be those of tuberculosis, and the inactive disease status. In the study group of reactivated cases, patients were active a mean of 684 days with a range of 200 to 2785 days. The control group was active for 674 days with a

range of 200 to 2190 days. There is no significant difference between the two groups.

The mean length of time between the first positive sputum examination and the last positive sputum examination was also calculated for each group. The study group had a positive sputum for a mean of 362 days with a range of 10 to 2400 days. The control group was positive for 296 days with a range of 10 to 1800 days. This difference of 93 days is not statistically significant.(P=.38).

A more critical examination of the length of sputum positivity is the time interval of conversion from positive to negative during chemotherapy. In each group, the mean average number of days from the beginning of chemotherapy to the last positive sputum was calculated. The conversion time under chemotherapy in the study group was 226 days with a range of 10 to 2400 days and was 179 days in the control group with a range of 10 to 1155 days. This difference of 47 days is not statistically significant.(P=.62).

C. TREATMENT WITH ANTI-TUBERCULOSIS DRUGS

The total number of days of chemotherapy was tabulated for patients in both groups. This included chemotherapy of any type which was administered during a patient's hospitalization as well as during follow-up study in the out-patient departments. Chemotherapy was received by the study group for a mean of 698 days with a range of 128 to 3170 days and by the control group for a mean of 766 days with a range of 251 to 3285 days. This difference of 67 days is not statistically significant. (P=.62).

Continuity of chemotherapy including both hospital and out-patient department treatment was also studied. In the study group, of reactivated cases, 3 patients (7.5%) discontinued chemotherapy for periods ranging from 10 to 240 days with a mean of 130 days. In the control group, 7 patients

(17.5%) discontinued chemotherapy for periods ranging from 15 to 575 days with a mean of 110 days.

The amount of isoniazid received by reactivated and non-reactivated cases was calculated and compared. In each group, 35 of 40 patients received isoniazid in their chemotherapy regimen. Isoniazid administered in the hospital as well as at home was combined to obtain the total amount of isoniazid which had been received by each patient. In almost all cases, the patients were also taking other drugs, mainly PAS and/or streptomycin. It was found that the study group received a total mean dosage of 202.9 grams of isoniazid with a range of 38 to 1021 grams while the controls received a mean dosage of 189.5 grams of isoniazid with a range of 13 to 518 grams. This difference of 13.4 grams is not statistically significant, (P=.72). It was interesting that there is no significant difference between these two groups, but not surprising, since the average number of days of chemotherapy is similar in both groups.

D. INDEX OF THERAPEUTIC RESPONSE TO TREATMENT

WEIGHT GAIN. The parameter of weight gain was examined in each group and used in this study as an index of response to treatment. Each patient was weighed monthly to evaluate the progress of his clinical course. At the time of discharge, the group of reactivated cases had gained a mean of 12.4 pounds with a range of 0 to 53 pounds. In contrast, the control group had a mean weight gain of 20.1 pounds with a range of 0 to 61 pounds. This difference of 7.7 pounds is statistically significant ($P < .01$). However, there was no knowledge of the patient's ideal body weight in relation to the amount of weight gained nor was height recorded. As shown in Table 9, 3 patients in the study group failed to gain weight and no information was

available on 7 patients; in the control group, 2 patients failed to gain weight, and there was no information on 2 patients.

PERCENT OF SPUTUM POSITIVITY. In the study group, an attempt was made to develop an index of clinical findings which might alert the physician to the possibility of reactivation of pulmonary tuberculosis infection. Accordingly, patients were studied in relation to patterns of sputum positivity. At the Mt. Morris Hospital, sputum cultures are collected for three consecutive days following the admission of each patient and usually once monthly thereafter. Since all patients in each group eventually became inactive, their sputum necessarily converted from positive to negative. In an attempt to determine the pattern of final sputum conversion from positive to negative, the percent of positive sputum cultures was calculated for each individual to classify his conversion pattern. The percent of positivity is the ratio of the number of positive cultures from the first positive to the last positive culture to the total number of cultures collected from the first positive to the last positive culture. For example, if a patient had his first three cultures positive and then remained negative for the remainder of his sputum examinations, the percent of positivity would be 3 positive cultures over 3 total cultures from the first positive to the last positive, or 100%. On the other hand, if a patient had his initial 3 cultures positive and then had 5 monthly negative cultures followed by 1 positive culture before his sputum became repeatedly negative again, his percent of positivity would be 4/9, or 44%. It is apparent that for this index to have meaning, regular sputum cultures must be performed so that equal time intervals are present between examinations. For example, at the end of ten months of treatment, each patient should have had recorded three initial sputum examinations and nine subsequent monthly examinations. This exemplified pattern was recorded for most patients, but there probably were some exceptions that were not carefully evaluated

when this information was collected. Thusly, conclusion obtained from these results can be questioned.

Each patient in both study and control groups was evaluated for the percent of sputum positivity and the results are summarized in Table 10. According to this analysis, 13 patients (32.5%) in the study group had a percent of positivity of less than 75% whereas, in the control group only 5 patients (12.5%) had a percent of sputum positivity of less than 75%. The difference of 20% between the two groups is statistically significant.(P=.03).

CLINICAL COURSE OF STUDY AND CONTROL GROUPS FOLLOWING HOSPITALIZATION

A. CONDITIONS FOR DISCHARGES FROM HOSPITAL

At the Mt. Morris Hospital, the conditions for discharge of a patient can be considered in 5 categories: 1) maximum hospital benefit (MHB); 2) personal reasons with or without consent of the clinical staff; 3) against medical advice (AMA); 4) absent without authorized leave (AWOL); and 5) disciplinary reasons. It was found in this study that 35 patients (87.5%) of the study group and 34 patients (85.6%) of the control group were discharged with maximum hospital benefit. These findings are depicted in Table 11.

B. ACTIVITY OF DISEASE AT TIME OF DISCHARGE

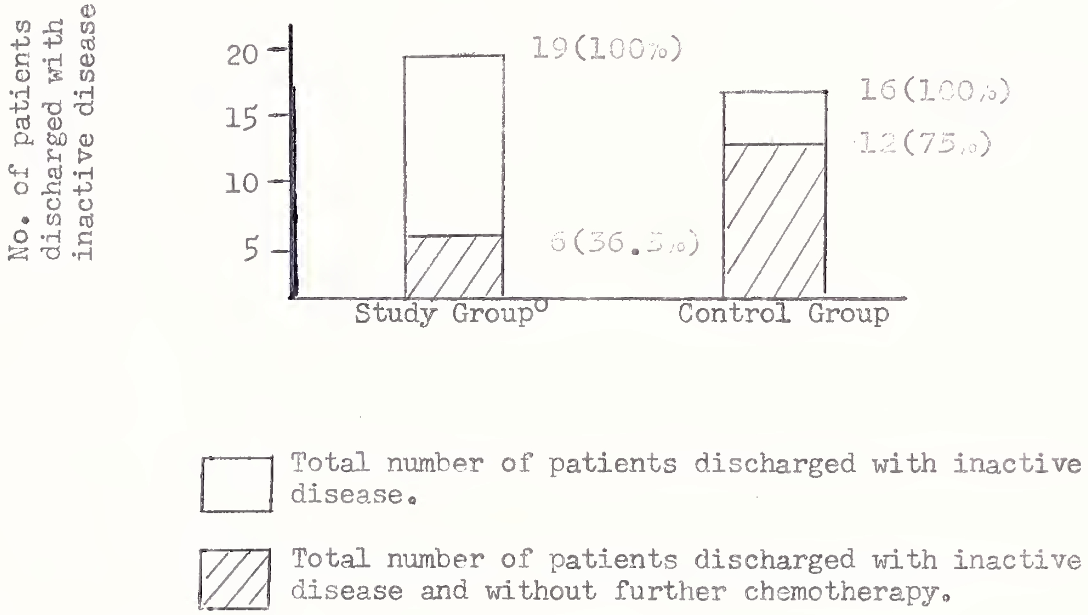
At the time of discharge from the hospital, 19 of 40 patients (47%) of the study group were considered to have inactive disease whereas, in the control group, 16 of 40 patients (40%) were inactive at discharge. These results are shown in Table 12. No difference was observed in the age distribution of these two groups nor was there appreciable difference in the prevalence of emphysema or other concomitant disease.

C. USE OF CHEMOTHERAPY ON DISCHARGE

When patients are discharged from the hospital they often continue chemotherapy for some time as an outpatient. It was shown that in the study group only 7 patients (17.5%) could be discharged without further chemotherapy whereas, in the control group 14 patients (35%) could be discharged without further chemotherapy. This difference is not statistically significant.($P=.08$). Of the 7 patients in the study group who were discharged without further chemotherapy, it was found that 6 of these 7 patients (85%) had inactive disease. Similarly, in the control group, of the 14 patients discharged without further chemotherapy, it was found that 12 of these 14 patients (85%) had inactive disease. These findings suggest that discontinuation of chemotherapy at discharge may mean inactive disease; however, it cannot be concluded that the converse, i.e., that inactivity of the infection at discharge of the patient implies discontinuation of therapy, is true. This point is shown in Table 13 which compares inactivity of disease at discharge to discontinuation of chemotherapy. In the study group, 19 patients (47.5%) were inactive at discharge and in control group 16 patients (40%) were inactive at discharge. However, in the study group, only 6 of these 19 inactive patients (36.5%) were discharged without further chemotherapy whereas, in the control group 12 of 16 inactive patients (75%) were discharged without further chemotherapy. This difference of 38.5% is statistically significant.($.02 < P < .05$). This comparison is shown in the following graph.

GRAPH NO. 1

COMPARISON OF INACTIVE DISEASE STATUS AND DISCONTINUATION OF CHEMOTHERAPY IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.



°Reactivated cases.

Such differences suggest that inactive disease status at discharge was associated with discontinuation of chemotherapy in the control group, but for some reason inactivity at discharge was not associated with discontinuation of chemotherapy in the study group.

An attempt was made to evaluate patients' adherence to discharge recommendations, Although this was a subjective evaluation and no apparent disregard for discharge recommendations in various categories was found in either group. The most objective parameter which could be evaluated was whether patients took their prescribed chemotherapy, and even this was often difficult to determine. In the study group, 8 patients (20% failed to continue their recommended chemotherapy while 6 patients (12.5%) in the control group failed to continue.

D. USE OF CHEMOTHERAPY AFTER THE INACTIVE STATUS

The number of days of chemotherapy after patients had reached the inactive status was calculated for each group. Most patients received their chemotherapy after becoming inactive through the outpatient department of the hospital. The mean number of days of use of chemotherapy after the inactive status in the study group was 176 days with a range of 0 to 820 days and in the control group was 215 days with a range of 0 to 2000 days. This difference of 39 days is not statistically significant (P=.60). In the study group, 10 patients (25%) received no chemotherapy after they became inactive, and in the control group 15 patients (37.5%) received no chemotherapy after they reached the inactive status. This difference also is not statistically significant (P=.22).

E. TIME OF REACTIVATION OF DISEASE

In the study group, it was found that reactivation of disease occurred on the average 660.50 days after the inactive status with periods ranging from 60 to 1800 days.

DISCUSSION

Prior to the advent of chemotherapy, there were numerous factors which predisposed to reactivation of pulmonary tuberculosis, the most important being: 1) extent of disease, 2) duration of hospitalization, and 3) patient cooperation. It has been shown in numerous studies that reactivation and relapse were more common the more advanced the extent of pulmonary disease[1,2]. It was also shown that patients having bilateral pulmonary disease relapsed more frequently (twice as common) than did those with unilateral disease[2]. Relapse also seemed to be independent of age[2]. However, since the widespread use of anti-tuberculosis drugs during the past 15 years, little recent attention has been directed to the factor or factors currently leading to reactivation of cases of pulmonary tuberculosis treated with these agents.

In this study, it has been possible to compare certain factors which may play a role in reactivation of pulmonary tuberculosis in a group of 40 patients and 40 matched controls in whom reactivation of disease did not occur. These two groups were matched in 5 categories: 1) age, 2) sex, 3) race, 4) presence or absence of isoniazid in chemotherapy regimen, and 5) use of resectional surgery.

In an attempt to correlate all the factors that have been compared, it is difficult, if not impossible, to delineate the factor or factors responsible for reactivation of previously drug-treated inactive pulmonary tuberculosis. The differences in those areas which were compared were in most cases not statistically significant, but there were several statistically significant differences.

In interpreting the significant results of this study, it is assumed that the patients in each group were essentially of the same background;

had similar disease; and received essentially similar standard treatment. The results, as well as can be interpreted, substantiate these assumptions. In regards to previous history, it was found that there was no significant difference between the groups in the presence of concomitant disease, respiratory symptoms on admission, past history of tuberculosis, marital status, extent of tuberculous infection, or presence of pulmonary cavitation. There were also no significant differences in the number of days these patients were in the hospital, the continuity of their hospitalization, the total time of their active pulmonary disease, the total time of sputum positivity, the time of sputum conversion under chemotherapy, the total days of chemotherapy received, the continuity of chemotherapy, the amount of isoniazid therapy which they received, and the number of days of chemotherapy which they were given after reaching an inactive status. It is also assumed that the patients in both groups received a similar diet while in the hospital.

In terms of the objectives of this study, the findings indicate that weight gain in the hospital may be a reliable prognostic index concerning subsequent reactivation of pulmonary tuberculosis infection. Gain in body weight can also be interpreted as an index of clinical response to treatment. It was found that at the time of discharge after an equal time in the hospital, with a similar diet, the study group of reactivated cases had gained a mean of 12.4 pounds with a range of 0 to 53 pounds while the control group gained a mean of 20.1 pounds with a range of 0 to 61 pounds. This difference of 7.7 pounds is statistically significant ($P < .01$). This difference suggests that the clinical response was different in the two groups even though patients in each group attained an inactive status in a similar time. Inactive disease status is based on radiological and

bacteriological information rather than clinical impression.

In the Madras study[16], certain facts were obtained regarding diet and weight gain. In comparing patients treated at home and in the hospital, it was found that although there were obvious measurable difference in the quality of their diets, there was no difference in attaining quiescent disease status at the end of one year. However, bacteriological conversion to negativity did occur more rapidly in the sanatorium patients. The average weight gain for a 12-month period was 19.8 pounds for the sanatorium patients and 10.8 pounds for the home patients. This difference of 9 pounds seems to be significant but not associated with differences in clinical response at the end of one year. However, in the present study, it is assumed that the diet in each group was similar with no obvious discrepencies as there was in the Madras study, and thus, the failure of the reactivated group to gain weight can be interpreted as an inadequate clinical response rather than an inferior diet. Thus, using weight gain as an index of the clinical response to treatment, it can be concluded that in this study, the control group of non-reactivated cases did have a better clinical response than did the study group of reactivated patients.

Another finding which suggests a poor clinical response to treatment is the comparison of the status of disease activity and the continuation of chemotherapy at the time of discharge. As was shown in the results, it seemed initially that inactive disease at discharge was an important criteria for discontinuation of chemotherapy. However, when the number of patients who were inactive at discharge is compared to the number of patients who were allowed to discontinue chemotherapy, certain differences were observed. In the study group, 19 patients were discharged with inactive disease but in

only 6 (36%) of these 19 patients was chemotherapy discontinued. In the control group, 16 patients were considered to be inactive at discharge, and in contrast to the study group, 12 (75%) of these 16 patients were permitted to discontinue chemotherapy. This 38.5% difference is statistically significant ($.02 < P < .05$). It can be concluded that although almost half of the reactivated patients were inactive at discharge, the clinical staff at Mt. Morris Hospital discontinued chemotherapy in only 36% of these patients whereas, in the control group 75% of 16 inactive patients were discharged without further chemotherapy. The reason for the continuation of chemotherapy in the study group patients is not clear, however, it can be hypothesized that clinical evaluation of the response of the patients to treatment was such that continuation of chemotherapy was deemed necessary.

Another parameter which may be used to determine clinical response is the percent of sputum positivity. As explained previously, this is the ratio of the number of positive sputum cultures to the total number of cultures taken from the first positive culture to the last positive culture. In this study, 13 patients (32.5%) among reactivated patients had a sputum positivity ratio of less than75% whereas, in the control group only 5 patients (12.5%) had a sputum positivity ratio of less than 75%. This difference of 20% was found to be statistically significant ($P = .03$). These observations suggest that the patients whose disease later became reactivated converted their sputum to negativity in a sporadic manner and showed a pattern of positive sputum cultures intermixed with negative sputum cultures. On the other hand, the control patients generally seemed to convert to negative and remained so without demonstrating intermittent positive sputum cultures. This may mean that the reactivated group did not respond to treatment as completely

as the control group even though both groups converted to negativity under chemotherapy during the same time period. The limitations of the collection of the data pertaining to the percent of sputum positivity was mentioned in the results; however, if further study in this area proved the validity of the percent of sputum positivity, the value of this observation as prognostic aid would be greatly increased.

An evaluation of the utilization of chemotherapy in this study revealed that there was no significant difference in the number of days of chemotherapy which each group received; likewise, the total amount of isoniazid received by each group was similar. Katz[14] found that treatment with isoniazid alone, which was continued for two years after inactivity, lowered the reactivation rate in 129 patients to 2.5% in the study group compared to 5% in the controls. In the Madras, India, study, it was shown that isoniazid alone administered for one year after quiescence in patients having no residual cavitation, helped to prevent relapse. In 103 patients with non-cavitating, quiescent disease, the relapse rate was 0% in the isoniazid group and 9% in the placebo-treated group ($P < .005$). However, it was also shown that treatment with isoniazid alone for 2 years after quiescence was no more efficacious than 1 year of treatment after quiescence of active disease. This was demonstrated by treating 30 patients and 30 controls with isoniazid and placebo; in both groups, the relapse rate was 0%. It has not been shown in any retrospective study that reactivated patients received significantly less chemotherapy than control patients.

In the present study, there were numerous host and environmental factors which were common to both groups. In this regard, it was of interest that there was an equal distribution of the extent of disease (P_1, P_2, P_3) in each group. This contrasts sharply to the findings during the pre-chemotherapy.

era where it was clearly shown that relapse was dependent upon the extent of disease and occurred much more frequently in those patients with far-advanced disease. However, in the present study, since patients were matched for age, reactivation seemed to be independent of extent of disease only among individuals of similar age.

Another finding related to the extent of disease is the presence or absence of pulmonary cavitation. These differences as well as the presence of bilateral pulmonary disease were equally distributed between both groups and had no apparent effect upon reactivation of disease.

In this study, the length of hospitalization was similar in both reactivated patients and controls. Also, there was no difference in the prevalence of concomitant disease in both groups which included emphysema, silicosis, diabetes mellitus and extra-pulmonary tuberculosis. This result can be questioned because there was no way of comparing the severity of any of these diseases.

Among the factors which were not possible to study in this group of patients, several of importance deserve mention. The first is determination of the drug sensitivity of the infecting strain of tubercle bacillus. Sensitivity of the organism to the major antituberculosis drugs is known to be a factor in the therapeutic response to treatment and is thought to be a factor in relapse of the disease[15]. In this study, the drug sensitivity was not known in many cases, and thus could not be evaluated. It is also known that often patients respond to the prescribed drug although the in vitro sensitivity test shows the organism to be resistant to the drug[6,17]. It has also been observed that a single sensitivity test may show the organism to be resistant whereas, a subsequent test may indicate sensitivity, thus making the interpretation of the conflicting data quite difficult.

Another area which could not be accuately evaluated because of lack of

information was the home environment and events in the lives of the patients after discharge from the hospital. Even though in most cases, the patients were followed in the outpatient department, no objective evaluation could be made regarding the patients' environment. Additional study of environmental influences on a patient's disease may provide some important leads in the study of reactivation of adequately treated cases of pulmonary tuberculosis.

SUMMARY AND CONCLUSIONS

1. The purpose of this study is to evaluate determinants which may be important in reactivation of previously drug-treated inactive cases of pulmonary tuberculosis. This is a retrospective study of 40 reactivated patients and 40 control patients. Both groups had pulmonary tuberculosis, were drug-treated, and reached the inactive status. The study group patients reactivated within a five-year period and the controls remained inactive for at least five years. The two groups were matched in five categories: 1) age, 2) race, 3) sex, 4) use of resectional surgery, and 5) presence or absence of isoniazid in the chemotherapy regimen. Since these areas were matched, they could not be compared and evaluated. Also not evaluated because of lack of information was occupation; smoking habits; drinking habits; educational background; an objective evaluation of the patient's life after becoming inactive; and most important, drug sensitivity of the organism.

2. There was a significant difference in weight gain during hospitalization between the two groups: the reactivated study group gained 12.4 pounds whereas, non-reactivated controls gained 20.1 pounds. This 7.7-pound difference is statistically significant ($P < .01$).

3. In the group of reactivated cases, 19 patients were discharged with inactive disease but in only 6 (36%) of these was chemotherapy discontinued.

In the control group, 16 patients were discharged with inactive disease but in contrast to the reactivated cases, 12 (75%) of these 16 patients were advised to discontinue chemotherapy. This 38.5% difference was found to be significant ($.02 < P < .05$).

4. In the study group, 13 patients (32.5%) had a percent of sputum positivity of less than 75% whereas, in the control group only 5 patients (12.5%) had a percent of sputum positivity of less than 75%. This difference of 20% is statistically significant ($P = .03$).

5. No differences of significance were found between the reactivated and control groups in the following areas: extent of disease; presence or absence of cavitating lesions; concomitant disease; marital status; past history of tuberculosis; duration of hospitalization; continuity of hospitalization; total duration of active disease; total time of positive sputum; conversion time to negativity under chemotherapy; days of chemotherapy; continuity of chemotherapy; amount of isoniazid administered; reason for discharge; adherence to discharge medical recommendations; and days of treatment after attaining an inactive status.

TABLE NO. 1

AGE, SEX AND RACIAL CHARACTERISTICS OF REACTIVATED CASES OF PULMONARY TUBERCULOSIS AND CONTROLS.

Age Distribution			Males in Study[o] and Control Groups				Females in Study[o] and Control Groups			
			White		Negro		White		Negro	
Age in Years*	No.	%	No.	%	No.	%	No.	%	No.	%
< 30	3	7.5	2	5	0	0	1	2.5	0	0
30-39	3	7.5	2	5	1	2.5	0	0	0	0
40-49	5	12.5	2	5	1	2.5	2	5.0	0	0
50-59	11	27.5	8	20	1	2.5	2	5.0	0	0
> 60	18	45.0	17	42.5	0	0	1	2.5	0	0
TOTALS	40	100	31	77.5	3	7.5	6	15.0	0	0

* Age determined at time of inactivity.

[o] Reactivated cases.

TABLE NO. 2

USE OF RESECTIONAL SURGERY AND CHEMOTHERAPY WITH ISONIAZID IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS

		Resectional Surgery in Patients in Study[o] and Control Group				Patients with INH in Chemotherapy Regimen in Study[o] and Control Groups			
Age in Years	No.	No. with Surgery	%	No. without Surgery	%	No. with INH	%	No. without INH	%
< 30	3	0	0	3	7.5	3	7.5	0	0
30-39	3	2	5.0	1	2.5	2	5.0	1	2.5
40-49	5	2	5.0	3	7.5	3	7.5	2	5.0
50-59	11	2	5.0	9	22.5	10	25.0	1	2.5
> 60	18	0	0	18	45.0	17	42.5	1	2.5
TOTALS	40	6	15.0	34	85.0	35	87.5	5	12.5

*Age determined at time of inactivity.

[o] Reactivated cases.

TABLE NO. 3

COMPARISON OF MARITAL STATUS AMONG MALES AND FEMALES HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Marital Status	Patients with Reactivated Disease				Control Group Patients			
	Male		Female		Male		Female	
	No.	%	No.	%	No.	%	No.	%
Single	8	20.0	3	7.5	10	25.0	3	7.5
Married	14	35.0	1	2.5	14	35.0	3	7.5
Separated	6	15.0	1	2.5	2	5.0	0	0
Divorced	3	7.5	0	0	3	7.5	0	0
Widowed	3	7.5	1	2.5	5	12.5	0	0
TOTALS	34	85.0	6	15.0	34	85.0	6	15.0

NOTE:

Percentage of divorced and separated patients in study and controls:

Study° patients	25.0%
Control patients	12.5%

Standard error of the difference = 8.6

Observed difference/standard error of difference 12.5/8.6 = 1.46

P value ≈ .14

Not statistically significant

°Reactivated cases.

TABLE NO. 4

PREVALENCE OF PULMONARY EMPHYSEMA AND CONTROL IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

		Emphysema Present				Emphysema not Present			
Age in Years*	No.	Study° Group Patients		Control Group Patients		Study° Group Patients		Control Group Patients	
		No.	%	No.	%	No.	%	No.	%
< 30	3	0	0	0	0	3	7.5	3	7.5
30-39	3	0	0	0	0	3	7.5	3	7.5
40-49	5	1	2.5	1	2.5	4	10.0	4	10.0
50-59	11	3	7.5	5	12.5	8	20.0	6	15.0
> 60	18	9	22.5	4	10.0	9	22.5	14	35.0
TOTALS	40	13	32.5	10	25.0	27	67.5	30	75.0

*Age determined at time of inactivity.
°Reactivated cases.

NOTE:
Observed difference of 7.5% (32.5 - 25.0) is not statistically significant.

P= .46

TABLE NO. 5

PREVALENCE OF DIABETES MELLITUS, SILICOSIS, AND EXTRA-PULMONARY TUBERCULOSIS IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Associated Disease Process		Study[o] Group Patients		Control Group Patients	
		No.	%	No.	%
Diabetes Mellitus	Present	1	2.5	5	12.5
	Absent	39	97.5	35	87.5
Silicosis	Present	2	5.0	3	7.5
	Absent	38	95.0	37	82.5
Extra-Pulmonary Tuberculosis	Present	1	2.5	4	10.0
	Absent	39	97.5	36	90.0

[o] Reactivated cases.

TABLE NO. 6

COMPARISON OF EXTENT OF PULMONARY TUBERCULOSIS IN PATIENTS HAVING REACTIVATED PULMONARY TUVERCULOSIS AND CONTROLS.

Age in Years*	No.	Study°Group						Control Group					
		Min.(P_1)		Mod.adv.(P_2)		Far-adv.(P_3)		Min.(P_1)		Mod.adv.(P_2)		Far-adv.(P_3)	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 30	3	1	2.5	2	5.0	0	0.0	0	0.0	2	5.0	1	2.5
30-39	3	0	0.0	1	25.0	2	5.0	1	2.5	1	0.5	1	2.5
40-49	5	1	2.5	3	7.5	2	5.0	1	2.5	3	7.5	1	2.5
50-59	11	1	2.5	4	10.0	5	12.5	3	7.5	4	10.0	4	10.0
> 60	18	5	12.5	10	25.0	3	7.5	3	7.5	10	25.0	5	12.5
TOTALS	40	8	20.0	20	50.0	12	30.0	8	20.0	20	50.0	12	30.0

*Age determined at time of inactivity.
°Reactivated cases.

NOTE:

P_1 = Minimal pulmonary tuberculosis.
P_2 = Moderately advanced pulmonary tuberculosis.
P_3 = Far-advanced pulmonary tuberculosis.

See Appendix I.

TABLE NO. 7

COMPARISON OF BILATERAL AND UNILATERAL PULMONARY TUBERCULOSIS IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Age in Years*	No.	Patients with Bilateral Disease				Patients with Unilateral Disease			
		Study[o] Group		Control Group		Study[o] Group		Control Group	
		No.	%	No.	%	No.	%	No.	%
< 30	3	0	0	1	2.5	3	7.5	2	5.0
30-39	3	1	2.5	1	2.5	2	5.0	2	5.0
40-49	5	3	7.5	4	10.0	2	5.0	1	2.5
50-59	11	9	22.5	7	17.5	2	5.0	4	10.0
> 60	18	12	30.0	14	35.0	6	15.0	4	10.0
TOTALS	40	25	62.5	27	67.5	15	37.5	13	32.5

*Age determined at time of inactivity.

o Reactivated cases.

TABLE NO. 8

COMPARISON OF PRESENCE OF CAVITATION OF PULMONARY PARENCHYMA IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Age in Years*	No.	Cavitation Present				Cavitation not Present			
		Study[o] Group		Control Group		Study[o] Group		Control Group	
		No.	%	No.	%	No.	%	No.	%
< 30	3	2	5.0	2	5.0	1	2.5	1	2.5
30-39	3	3	7.5	2	5.0	0	0.0	1	2.5
40-49	5	3	7.5	3	7.5	2	5.0	2	5.0
50-59	11	5	12.5	5	12.5	6	15.0	6	15.0
> 60	18	7	17.5	7	17.5	11	27.5	11	27.5
TOTALS	40	20	50.0	19	47.5	20	50.0	21	52.5

*Age determined at time of inactivity.

o Reactivated cases.

TABLE NO. 9

COMPARISON OF MEAN WEIGHT GAIN DURING HOSPITALIZATION IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Age in Years*	No.** Studied	Average Weight Gain in Each Age Group in Study[o] Group (lbs.)	No. Studied	Average Weight Gain in Each Age Group in Control Group (lbs.)
< 30	3	15.3	3	44.0
30-39	3	4.3	3	9.0
40-49	4	12.2	5	22.2
50-59	10	15.0	11	20.2
> 60	13	11.7	1	16.8
TOTAL AVERAGE GAIN	33**	12.4	38**	20.1

* Age determined at time of inactivity.
** No information was available for 7 study patients and 2 control patients.
o Reactivated cases.

NOTE:

1) Mean weight gain in study[o] group 12.4 lbs.
control group 20.1 lbs.
2) Observed difference 7.7 lbs.

3) Standard deviation study[o] group 9.20
control group 12.24

4) Standard error of the difference 2.57

5) Observed difference/standard error of difference 7.70/2.57 = 3.00

6) P value: P <.01 Statistically significant.

TABLE NO. 10

COMPARISON OF PERCENT OF SPUTUM POSITIVITY IN PATIENTS HAVINC REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Percent of Positivity	Study[o] Group		Control Group	
	No.	%	No.	%
100 - 76%	25	62.5	35	87.5
75 - 51%	7	17.5	3	7.5
50 - 26%	5	12.5	2	5.0
25 - 0%	1	2.5	0	0
Not known	2	5.0	0	0
TOTALS	40	100	40	100

[o] Reactivated cases.

NOTE:

It is assumed that the 2 unknown patients in study[o] group are > 75% positivity.

Percentage of study[o] and control patients with percent of sputum positivity of less than 75%.

Study[o] patients	32.5%
Control patients	12.5%

Standard error of the difference = 9.1

Observed difference/standard error of difference 20.0/9.1 = 2.19

P value = .03 is statistically significant.

TABLE NO. 11

CONDITIONS FOR HOSPITAL DISCHARGE IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Condition for Hospital Discharge	Study° Group		Control Group	
	No.	%	No.	%
Maximum hospital benefit (MHB)	35	87.5	34	85.0
Personal reasons with consent	1	2.5	3	7.5
Personal reasons without consent	3	7.5	0	0
Against medical advice (AMA)	0	0	2	5.0
Absent without leave (AWOL)	0	0	1	2.5
Disciplinary	1	2.5	0	0
TOTALS	40	100	40	100

o Reactivated cases.

TABLE NO. 12

COMPARISON OF DISEASE ACTIVITY AT TIME OF DISCHARGE IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Age in Years*	No.	Patients with Inactive Disease at Time of Discharge				Patients with Active Disease at Time of Discharge			
		Study[o] Group Patients		Control Group Patients		Study[o] Group Patients		Control Group Patients	
		No.	%	No.	%	No.	%	No.	%
< 30	3	2	5.0	1	2.5	1	2.5	2	5.0
30-39	3	1	2.5	3	7.5	2	5.0	0	0
40-49	5	1	2.5	4	10.0	4	10.0	1	2.5
50-59	11	7	17.5	3	7.5	4	10.0	8	20.0
> 60	18	8	20.0	5	12.5	10	25.0	13	32.5
TOTALS	40	19	47.5	16	40.0	21	52.5	24	60.0

* Age determined at time of inactivity.

[o] Reactivated cases.

TABLE NO. 13

COMPARISON OF PATIENTS WITH INACTIVE DISEASE AT DISCHARGE AND THE CONTINUATION OF CHEMOTHERAPY IN PATIENTS HAVING REACTIVATED PULMONARY TUBERCULOSIS AND CONTROLS.

Age in Years*	No.	Patients Inactive at Discharge with Continued Chemotherapy				Patients Inactive at Discharge without Further Chemotherapy			
		Study° Group		Control Group		Study° Group		Control Group	
		No.	%	No.	%	No.	%	No.	%
< 30	3	1	2.5	0	0	1	2.5	1	2.5
30-39	3	0	0	0	0	1	2.5	3	2.5
40-49	5	1	2.5	1	2.5	0	0	3	7.5
50-59	11	4	10.0	1	2.5	3	7.5	2	5.0
> 60	18	7	17.5	2	5.0	1	2.5	3	7.5
TOTALS	40	13	32.5	4	10.0	6	15.0	12	30.0

*Age determined at time of inactivity.
o Reactivated cases.

NOTE:

Patients inactive at discharge without further chemotherapy:

Study° patients	36.5% of 19 patients
Control patients	75.0% of 16 patients

SEE TABLE 13 A.

TABLE 13A

CHI SQUARE CALCULATIONS FOR DIFFERENCES OBSERVED IN TABLE 13

	Inactive Patients at Discharge without further Chemotherapy	Inactive Patients at Discharge with further Chemotherapy	TOTALS
Study Group	6	13	19
Control Group	12	4	16
TOTALS	18	17	35

$$\chi^2 = \frac{35\left[\left|24 - 156\right| - 17.5\right]^2}{(18)\ (17)\ (16)\ (19)} = \frac{458,859}{93,024} = 4.93$$

P Value result = $.02 < P < .05$ is statistically significant.

The statistical significance of the difference between these percentages was tested by the chi-square test with a correction for continuity. The usual test used in the other tables was not used here because of the smaller number on which these percentages were based.

APPENDIX I

EXTENT OF DISEASE

Extent of disease is determined by radiologic examination and is classified as minimal, moderately advanced, or far-advanced in accordance to the standards of the National Tuberculosis Association.

1) Minimal. Minimal lesions include those which are of slight to moderate density but which do not contain demonstrable cavitation. They may involve a small part of one or both lungs but the total extent, regardless of distribution, should not exceed the volume of lung on one side which is present above the second chondrocostal junction and the spine of the fourth or the body of the fifth thoracic vertebrae.

2) Moderately Advanced. Moderately advanced lesions may be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight to moderate density which may extend throughout the total volume of one lung, or the equivalent in both lungs; dense and confluent lesions which are limited in extent to one-third the volume of one lung; total diameter of cavitation, if present, must be less than 4 cm.

3) Far-advanced. This term is used to describe lesions which are more extensive than moderately advanced.

APPENDIX II

ACTIVITY STATUS

The stages of activity of pulmonary tuberculosis are based largely on roentgenographic and bacteriologic factors, and their duration. Disease is classified as active, quiescent, or inactive in accordance to the standards of the National Tuberculosis Association.

1) Active.

Bacteriologic: Tubercle bacilli demonstrated by any method in the sputum, gastric aspirates, or tracheal aspirates denote active tuberculosis.

Roengenographic: An active status exists if the probability of change is obvious on examination of a single chest x-ray, or if change for better or worse is demonstrable on serial x-rays at intervals of six months or less. The presence of tuberculous empyema, bronchopleural fistula, or active endobronchial tuberculosis requires that associated pulmonary tuberculosis be considered as active.

2) Quiescent.

This term requires negative bacteriologic findings and stable or improving lesions visible by x-ray but it allows the presence of cavitation. Bacteriologic examination must be negative for six months. This category includes the "open negative" lesions which are now being seen with increasing frequency.

3) Inactive.

The bacteriologic test must be negative by all methods for at least 6 months. The x-ray examination must also be stable for at least six months, and no cavitation may be present. The required period of negative

bacteriologic status and the duration of stable, non-cavitary, radiologic findings coincide, but the classification of inactive cannot be used until both have been present for six months.

APPENDIX NO. III

STATISTICAL METHODS

I. DIFFERENCES BETWEEN MEANS

1) Calculation of Standard Deviations

X = individual observation

$\bar{X}$ = mean of this observation

N = number of observations

Through the following relationships, the standard deviation is calculated:

$$\text{Sum } (X - \bar{X})^2 = \text{Sum } X^2 - (\text{Sum } X)^2 / N$$

$$\text{Standard deviation} = \sqrt{\frac{\text{Sum } X^2 - (\text{Sum } X)^2 / N}{N-1}}$$

2) Calculation of standard error of this difference between means:

S = study group

C = control

$$\text{Standard error of the difference} = \sqrt{\frac{(\text{ST.DEV}_s)^2}{N_s} + \frac{(\text{ST.DEV}_c)^2}{N_c}}$$

3) Z = observed difference/calculated standard error of difference

The value of Z is referred to tables of area under the normal curve for corresponding P-values.

4) P Value

The area under the normal curve for values of Z equal to or greater than the value observed, disregarding sign.

II. DIFFERENCES BETWEEN PROPORTIONS

1) Calculation of standard error of the differences between proportions:

p = percentage in the universe in one category, i. e., having a property.

q = percentage in the universe in the other category, i. e., not having that property.

Standard error of the difference $= \sqrt{\frac{p \times q}{N_s} + \frac{p \times q}{N_c}}$

N_s = number in study group

N_c = number in control group

2) Z = observed difference/calculated standard error of difference. Same as in differences between means.

3) P Value Same as in differences between means.

APPENDIX IV

STATISTICAL CALCULATION TABLE FOR OBSERVATIONS WHICH ARE NOT IN TABLE FORM.

Observations which are being compared	No. of observations N		Mean Value $\bar{X}$	Standard Deviation (ST.DEV.)	Estimated Variances of the Mean $\frac{(\text{ST.DEV.})^2}{N}$	Sum of Study° and Control Estimated Variance of the Mean	Standard Error of the Difference between the Means	$\frac{\text{Observed Difference}}{\text{Standard Error of the Difference}}$ = Z		P Value P < .05 is Statistically Significant
Total time of positive sputum examinations	Study°	40	361.75	540.00	7,300.00)	11,500.00	107.00	$\frac{92.80}{107.00}$	.88	.38
	Control	40	268.95	408.00	4,170.00)					
Chemotherapy to last positive culture (conversion time)	Study°	40	226.12	542.00	7,350.00)	9,000.00	94.80	$\frac{47.25}{94.80}$	.50	.62
	Control	40	178.88	259.00	1,690.00)					
Total days of chemotherapy	Study°	40	698.60	579.00	8,400.00)	18,500.00	136.00	$\frac{67.57}{136.00}$	.50	.62
	Control	40	766.17	634.80	10,100.00)					
Total days of chemotherapy after inactive status	Study°	40	176.25	233.40	1,360.00)	5,400.00	73.48	$\frac{39.15}{73.48}$	.53	.60
	Control	40	215.40	401.20	4,040.00)					
Amount of isoniazid in grams	Study°	35	202.90	196.00	1,096.00)	1,448.00	37.9	$\frac{13.4}{37.9}$	.36	.72
	Control	35	189.50	111.00	352.00)					

o Reactivated cases.

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